

Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-40 are pending in the application, with claims 21, 30 and 40 being the independent claims. Claims 1-20 have been withdrawn. New claim 40 is sought to be added. Support for these amendments and for new claim 40 may be found throughout the specification and claims as originally filed, such as, *inter alia*, in paragraph [0068] and the Examples. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejections under 35 U.S.C. § 112

The Examiner has rejected claims 30-39 under 35 U.S.C. § 112, second paragraph, asserting that they are indefinite. (OA, page 3). More specifically, the Examiner asserts that the detection limit of any particular assay recited in claim 30 "depends on the conditions under which it is performed as well as the ingredients used," and therefore "the level of impurities detected will depend on where and how the assay is performed." (OA, page 3). Further, the Examiner notes that the Applicants did not recite specific conditions and cutoff values that would result in undetectable levels of impurities for the listed assays. (OA, page 3). Applicants respectfully traverse this rejection.

The detection methods recited in claims 30-39 are not sensitive enough to detect the amounts of impurities that may be present in the DNA product of the present

invention, therefore it is unnecessary to include specific assay conditions in claim 30 to satisfy the definiteness requirement of 35 U.S.C. § 112. As explained in the specification of the present application, “[t]he DNA product produced by this manufacturing process is essentially free of, contains only trace levels of, or contains undetectable levels of host cell derived impurities.” (Specification at [0019]). Examples of such host cell derived impurities include, but are not limited to, RNA, protein, endotoxins, pyrogens and host chromosomal DNA. (Specification at [0019]). The specification also points out typical methods for measuring levels of DNA, RNA, protein or endotoxins: LAL assay, Southern blot assay, chromatography, Northern blot assay and ethidium bromide agarose analysis. (Specification at [0070]).

In this case, any impurities contained in the claimed DNA product are present in amounts so minute that LAL assay, Southern blot assay, chromatography, Northern blot assay and ethidium bromide agarose analysis are simply not sensitive enough to detect them *under any conditions*. Thus, recitation of assay conditions in claim 30 is unnecessary because the metes and bounds of the claims would be clear to a person of ordinary skill in the art in their current form.¹ Accordingly, claim 30 and any claims depending therefrom are sufficiently definite to satisfy 35 U.S.C. § 112, second paragraph. Reconsideration and withdrawal of this rejection is respectfully requested.

¹ In the February 2, 2008, Advisory Action, the Examiner asks why the Applicant is claiming detection techniques that cannot detect the levels of impurities in the purified DNA. The Applicant would like to point out that the claims are directed to a DNA product, as opposed to methods for detecting impurities in a DNA product. The recited detection techniques indicate the extremely high level of purity of the claimed DNA products, and therefore help to define the scope of the claims.

Rejections under 35 U.S.C. § 102

The Examiner has rejected claims 21 and 24-39 under 35 U.S.C. § 102(b) over U.S. Patent Application Publication No. 2001/0034435 A1 ("*Nochumson et al.*"). (OA, page 4). Applicants respectfully traverse this rejection.

Claim Interpretation

The Examiner asserts that the Applicants did not define the term "about X units," and therefore considers "any reasonable value below or above a given number X" to anticipate the term. (OA, page 3). Applicants respectfully disagree.

The recitation of "about" as it is used in the specification and presently-pending claims 21-29 would be understood by a person of ordinary skill in light of the technology embodied by the invention. *See W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1557, 220 USPQ 303, 316 (Fed. Cir. 1983) ("use of 'stretching . . . at a rate exceeding about 10% per second' in the claims is not indefinite."). Section 2173.05(b) of the MPEP states that "[i]n determining the range encompassed by the term 'about', one must consider the context of the term as it is used in the specification and claims of the application," citing *Ortho-McNeil Pharm., Inc. v. Caraco Pharm. Labs., Ltd.*, 476 F.3d 1321, 1326 81 USPQ2d 1427, 1432 (Fed. Cir. 2007).

In this case, both the specification and claims themselves set forth the ranges pertinent to the present invention. A person of ordinary skill in the art of DNA production would understand that the use of "about" with the recited numerical ranges merely allows for the small margin of error that may be associated with the instruments used to determine purity of the claimed product. More specifically, a person of ordinary skill in the art would realize that any significant expansion of the recited ranges would be

contrary to the high level of purity associated with the presently-claimed DNA product. Thus, the Examiner's assertion that "any reasonable value below or above a given number X is considered to anticipate this term" based on the use of "about" expands the scope of the term beyond its meaning as understood by those of ordinary skill in the art in light of the specification and claims. Reconsideration is respectfully requested.

Claims 21 and 24-39

The Examiner asserts that Nochumson *et al.* teach a plasmid DNA and pharmaceutical preparation that anticipates the ranges recited in claims 21 and 24-39. (OA, page 4). More specifically, the Examiner asserts that on page 8, [0099] of the published application, Nochumson *et al.* teach plasmid DNA preparation with 95% plasmid DNA and less than 5% RNA, an undetectable amount of RNA product, plasmid DNA preparations with 0.05% of host DNA (equivalent to 0.0005 µg of host DNA/µg of DNA product), less than 0.06% of protein (equivalent to 0.0006 µg/µg of DNA product), and less than 0.2EU/mg of endotoxin (equivalent to less than 0.0002 EU/µg). The Examiner concludes that Nochumson *et al.* anticipate the ranges recited in claims 21 and 28-39. (OA, page 4). Applicants respectfully traverse this rejection.

Solely to advance prosecution, and not in acquiescence of the Examiner's rejection, independent claim 21 has been amended to recite a DNA product comprising from about 95% to about 100% circular plasmid DNA, wherein said DNA product contains from about 0.00001% to about 0.0001% RNA; from about 0.00004 µg to about 0.002 µg host DNA per µg of DNA product; from about 0.00000001 µg to about 0.001 µg protein per µg DNA product; and wherein said DNA product contains from about 0.00001 to about 0.01 Endotoxin Units (EU) per µg DNA product.

Nochumson *et al.* do not anticipate presently-pending claims 21 and 24-29 because they do not disclose every a DNA product that contains from about 0.00001% to about 0.0001% RNA, as required by independent claim 21 and dependant claims 22-29. To anticipate a claim, the reference must teach *every* element of the claim. *See* MPEP § 2131 (citing *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987)). In order to anticipate claims, the recited subject matter must also be disclosed in the reference with “sufficient specificity” to constitute an anticipation under the statute. *See* MPEP § 2131.03. If the claims recite a narrow range and the reference teaches a broad range, the Federal Circuit has held in some cases that the narrow range is not disclosed with “sufficient specificity” to constitute an anticipation of the claims. *See id.*, *see also*, e.g., *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999, 78 USPQ2d 1417, 1423 (Fed. Cir. 2006)(The court held that a reference temperature range of 100-500°C did not describe the claimed range of 330-450°C with sufficient specificity to be anticipatory.)

In this case, the Examiner asserts that Nochumson *et al.* disclose a plasmid DNA composition comprising less than 5% RNA, which therefore anticipates any value between 0 and 5%. (OA, page 4). However, Nochumson *et al.* do not provide any data points or specific values within this broad range, but instead merely state that “less than 5% RNA” was present in one sample preparation that was found to contain 95% plasmid DNA. (*See* Nochumson *et al.* [0099]). Thus, it seems Nochumson *et al.* simply subtracted 95% from 100% to arrive at the 5% maximum instead of actually quantifying the amount of RNA in the sample.

In contrast, presently-pending claims 21-29 are directed to a DNA product with 0.00001% to 0.0001% RNA, and presently-pending claims 30-39 are directed to a DNA product that contains an amount of host cell derived impurities, including RNA, that is undetectable by any one of a group consisting of: LAL assay, Southern blot assay, chromatography, Northern blot assay, and ethidium bromide agarose analysis. Thus, the RNA present in the DNA product of claims 21-39 is at least several orders of magnitude less than the range picked by Nochumson *et al.* Accordingly, the broad range of 0 to 5% RNA in a DNA product is not sufficiently specific to anticipate the DNA product comprising 0.00001% to 0.0001% or undetectable amounts of RNA, as recited in presently-pending claims 21-39. Reconsideration and withdrawal of this rejection is respectfully requested.

Rejections under 35 U.S.C. § 103

The Examiner has rejected claims 22 and 23 under 35 U.S.C. § 103(a) over Nochumson *et al.* More specifically, the Examiner asserts that Nochumson *et al.* teach plasmid DNA preparation with less than 5% RNA (page 8, [0099]), but do not teach preparations with about 0.00001% to 0.0001% RNA or preparations with 0.0001% RNA,” but that a person of ordinary skill in the art could have prepared a DNA product with these levels through routine optimization. (OA, page 5). Applicants respectfully traverse this rejection.

The Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the cited art. *See In re Piasecki*, 745 F.2d 1468, 1471-72 (Fed. Cir. 1984). In order to establish a *prima facie* case of obviousness, the proper analysis is to first consider whether the following three criteria are met: (1) there must be some reason,

either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference (or references when combined) must teach or suggest all the claim limitations. MPEP § 2143.

In this case, Applicants respectfully assert that the Examiner has not demonstrated that Nochumson *et al.* would have had a reasonable expectation of success in producing a DNA product with 0.00001% to 0.0001% RNA as required by claims 22 and 23. Thus, at least the second criteria necessary to establish a *prima facie* case of obviousness has not been met.

As discussed above, there is no indication in Nochumson *et al.* that a person of ordinary skill in the art would have had a reasonable expectation of success in producing a DNA product within the range recited in claims 22 and 23. To the contrary, Nochumson *et al.* state that their isolated plasmid DNA product “is produced in a yield of at least 60% (preferably 70%, more preferably 80%, most preferably 90%).” (Nochumson *et al.* at [0034]). Thus, if Nochumson *et al.* are determining the amount of RNA by subtracting the DNA yield percent from 100% (as discussed above), their DNA products could have up to 40% RNA contamination. Example 9, which allegedly discloses an RNA assay, is prophetic and no other proof of low RNA contamination appears in the Nochumson *et al.* specification.

Nochumson *et al.* also admit that RNA is one of the two contaminants which may be “particularly troublesome” in plasmid DNA products, and yet they do not demonstrate a DNA product with specific RNA levels that are less than 5% of the product.

(Nochumson *et al.* at [0011]). The process described in the present specification was used by Applicants to produce the claimed DNA composition, which produces a DNA product with much lower contaminant levels than the process used by Nochumson *et al.*, including surprisingly low levels of RNA. The Examiner has not pointed to any evidence that the Nochumson *et al.* process could be somehow optimized to obtain the same high purity levels produced by Applicants' process. Nochumson *et al.* identified RNA contamination as troublesome, therefore it seems reasonable that they would have made every effort to optimize their DNA product, and yet they do not specifically report the low RNA levels recited in claims 22 and 23. As such, Applicants respectfully assert that the Examiner has not shown a reasonable expectation of success in arriving at the claimed invention based on the disclosure of Nochumson *et al.*, and therefore has not met her burden for establishing a *prima facie* case of obviousness. Reconsideration and withdrawal of this rejection is respectfully requested.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.


Amdt. dated Apr. 9, 2008 - 16 -
Reply to Advisory Action of February 6, 2008

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Appl. No. 10/719,978

Prompt and favorable consideration of this Amendment and Reply is respectfully
requested.

Respectfully submitted,

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Date: April 9, 2008

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